HISTORICAL MILESTONES

Historical Vignette Celebrating the 30th Anniversary of Diagnostic Ambulatory Electrocardiographic Monitoring and Data Reduction Systems

ELIOT CORDAY, MD, FACC
Los Angeles, California

The ambulatory electrocardiographic (ECG) monitor is a device developed approximately 30 years ago to detect, locate and document hemodynamic insufficiency states in target organs with compromised regional arterial circulations. These insufficiency states are usually silent until they are suddenly precipitated by secondary remote, hemodynamically significant cardiac arrhythmias, hypotensive states caused by internal hemorrhage or reduced cardiac output including cardiogenic shock. Insufficiency events cause serious regional dysfunction, resulting in transitory or permanent damage of the remote target organs (brain, heart, splanchic and renal) often causing paralytic ileus, gangrene of the gut or rectum, myocardial infarction or cerebral stroke.

During the closing ceremonies of the 3rd International Symposium on Holter Monitoring in Vienna (1), the cochairmen of the closing session—Fritz Kaindl (President of the Symposium Organizing Committee) and Heinz S. Weber (Secretary of the Program Organizing Committee)—honored me as one of the scientists who first described and documented critical hemodynamic insufficiency states, which cause sudden, recurrent, disabling clinical events that precipitate regional ischemic dysfunction of remote target organs. They remembered that I had also worked closely with Norman ("Jeff") Holter and his outstanding engineering staff during the formative years of the first clinically effective ambulatory electrocardiographic (ECG) monitoring system and asked that I prepare this historical vignette.

Norman Holter (Fig. 1)

Norman Jefferis ("Jeff") Holter, DSc and I first became acquainted in 1938 when we were appointed to serve on the editorial board of the Journal of Nuclear Medicine. Jeff was then 44 years old, a distinguished physicist who had served with the University of California Institute of Oceanography (Wilfred R. Glassock, Ray Cherry, Cliff Sanctuary).

Comprehensive experimental studies conducted in the author's laboratory over a period of years (1946–1971) proved that such remote ischemic states are often recurrent and can cause serious, irreparable damage, but whenever the cause of the regional ischemic state was treated promptly it could reverse the insufficiency state. Practical ambulatory ECG diagnostic monitors and data reduction systems were developed to diagnose these elusive precipitating pathophysiologic events that might coincide with the patient's symptoms and thus determine the most appropriate preventive therapy.

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Jeff Holter—the dynamic optimist. Jeff was a bright, happy, handsome, sociable and optimistic person with a dynamic personality and a warm sense of humor. He had been born and brought up in Helena, Montana. He received his advanced scientific training in California (AB in chemistry and MA in physics from University of California, Los Angeles, MS in chemistry from University of Southern California). Although his doctoral studies in California were interrupted by the pending war emergency in the early 1940s, two decades later he served as Vice Chancellor at the new University of California at La Jolla (later to be known as University of California, San Diego), and was awarded an honorary Doctor of Science degree from Montana State University. When his father, who was a much respected businessman, retired for reasons of health, Jeff left the field of research to manage the family business responsibilities and also established the Holter Research Foundation, a
small self-subsidized laboratory in Helena, so he could stay active in the field of research. At that time, he asked me to serve as a medical consultant to his radiotelemetry work. One day, in the early 1950s, the renowned pioneer cardiologist of that era, Paul Dudley White, visited Jeff in his laboratory in Helena and discussed Jeff's attempts to transmit ECG and electroencephalographic signals from space back to earth (6-13). White was impressed and shortly thereafter with Dr. White's encouragement Jeff received some financial support from the National Institutes of Health.

The Coronary Insufficiency Syndrome

Although he did not hold an MD degree, Jeff was a keen student of biologic science and kept up with current research. He leaned heavily on my experience because he was aware of my clinical research endeavors during 1946 and 1947, when I worked with Simon Dack and Arthur Master in New York (14-18). At that time, Master, Dack and their coworkers demonstrated that if a patient had coronary artery stenosis, it usually remained symptomatically silent because the collateral coronary circulation was sufficient to maintain vital regional nutrition. It also became clear that after a sudden increase in cardiac work or a sudden drop in systemic blood pressure, the collateral circulation would immediately fail to provide sufficient vital nourishment to the jeopardized myocardium. This ischemic state could be documented by cardiac enzyme release or ECG recordings, with the latter sometimes also exhibiting diagnostic ST segment depression and inverted T waves (14-18). I emphasized that although convenient diagnostic ambulatory monitoring techniques to detect such relatively silent triggering events were not yet available, it was already evident that if the precipitating causes of ischemia were treated promptly, the regional ischemic state might be rapidly reversed (18-27).

The studies by Master, Dack and coworkers had already popularized this syndrome, which they named "coronary insufficiency," as an intermediate functional form of myocardial ischemia existing between angina pectoris and myocardial infarction. Other insufficiency states of the heart, brain, gastrointestinal tract and kidney were first described and proved in my experimental laboratory at Cedars of Lebanon Hospital in the years from 1953 to 1968 (19-25). All such phantom states had one thing in common: they could be precipitated by relatively silent remote events. It was thus clear that ideally, these precipitating events should be identified and documented by an ambulatory ECG monitor in the patient's customary home or business environment (28).

Necessity Is the Mother of Invention

In light of these studies, Jeff realized that the newer trends in cardiology practice would require ambulatory ECG documentation. The original unwieldy apparatus (Fig. 2), consisting of a bulky ECG radio transmitter and heavy batteries (together weighing 85 lb) could not realistically be worn by a patient being monitored. Holter's engineers had been aggressively pursuing problem solving to make a lighter
discuss rebuilding a more practical system to document the brilliant senior engineer, Wilford Glasscock, to work with occlusion of the target organs. In 1962 Holler sent his mic syndromes, even in the absence of a frank vascular insufficiency states. In 1965, 1 emphasized to Holler the need to develop even more lightweight, more practical model as early as 1950. By 1952 the cumbersome amplifier and transmitter had been refined from an 85 lb unit to a 2.6 lb amplifier and transmitter, but it was reported that the FCC was not interested in licensing broadcast channels for medical purposes. I therefore recommended that he scrap the broadcast system and design a more practical monitoring and scanning analysis system.

In 1958 as a Journal of Nuclear Medicine editorial board meeting, Jeff brought along some elements of his cumbersome broadcast system. His research grant had lapsed and he was unable to assemble effective logistic systems that could provide for more convenient, practical clinical monitoring. He also was concerned that some of the general medical profession was disinterested and hostile because his studies were providing startling headlines to the press on medical breakthroughs but he was not a practicing doctor of medicine. He suggested that it was possible that the medical profession did not understand or agree with my concepts that "insufficiency states" could cause serious remote ischemic syndromes, even in the absence of a frank vascular occlusion of the target organs. In 1962 Halter sent his brilliant senior engineer, Wilford Glasscock, to work with my staff at the Cedars of Lebanon laboratory to demonstrate the hand-made version of the Halter Monitor system and discuss rebuilding a more practical system to document the precipitating causes of such insufficiency states. My staff and I were greatly convinced of the enormous possibilities of this device; however, Halter continued to question my enthusiasm and whether there was a real need for the documentation of what I described as "remote phantom pathophysiologic events" which were based on my personal experimental studies and clinical observations from 1948 to 1965.

I then redirected our basic animal research studies to attempt to document remote functional hemodynamic disturbances that might explain the pathophysiology of the "insufficiency states" (Fig. 3 and 4). We went on to record numerous other ECG abnormalities of cardiac arrhythmias with clinical findings that validated our experimental concepts (5,19-25,28-33). At last we could provide experimental proof from the animal laboratory plus clinical documentation that silent or remote regional myocardial insufficiency was factual. We could even document episodes of transient psychosis due to recurrent ventricular arrhythmias (5).

I emphasized to Halter the need to develop even more lightweight, noise-free, miniature recording circuitry that could fit into small recording containers and would permit practical documentation systems that could be conveniently carried by the ambulatory patient in the course of everyday events. I also recommended that Halter's engineers adapt more practical ECG magnetic tape recorder and playback systems capable of compressing 8 to 24 h of ECG or blood pressure data into a miniaturized recorder to make the ambulatory system more compatible with the native environment.

At that time, Halter realized that there was a need to provide other new data reduction systems so that busy practitioners would not be overwhelmed and thus discouraged by having to interpret miles of ECG recordings for each patient studied over a period of days (Fig. 5). This was to be the first step in planning a practical miniature tape recording and data reduction system to document evanescent arrhythmias, including conduction defects. The system would have to incorporate the elapsed time plus rapid real-time readout that would fit into the clinical chart for future reference, for full disclosure clear-cut documentation and recall.

The Electrocardiocorder Detects the Cause of Preventable Sudden Death

Jeff Halter remained concerned but not completely convinced that a more practical design of his outmoded and cumbersome radiotransmitter system was needed. But in 1961 when the more appropriate miniature ECG recording prototype was being completed by Halter's engineers, an incident occurred that suddenly changed his mind. In Helena
Three panels record oscilloscopic patterns of typical premature RR intervals of cardiac arrhythmias denoted as a picket fence. The three panels record oscilloscopic patterns of typical premature ventricular systole with compensatory pause (RSR), shortened pickets of atrial fibrillation (FIB), and irregularly sized pickets of atrial tachycardia (TACHY) and irregularly sized pickets of atrial fibrillation (FIB).

When the surgeon, who was operating while the ambulatory ECG was being recorded, suddenly died just as he was completing the operation. However, the ECG was not read until Jeff personally brought it to Los Angeles 1 week later for my interpretation with our new data reduction and readout system (Fig. 6). To our surprise, and that of the coroner, the ECG showed that Jeff’s friend had actually been having serious asymptomatic ST segment elevations and depressions, onset of extraordinarily high peaked T waves and on-and-off paroxysms of ventricular tachycardia and fibrillation and that one of these last paroxysms probably killed him (Fig. 6).

At last, Jeff concluded that the new prototype might be able to facilitate a clinically important and accurate diagnosis and prognosis for the patient at high risk of imminent sudden cardiac death. The fact that the monitor solved the mystery of an unexpected sudden death and clarified and documented the diagnosis encouraged us to move faster. Thus, from one sad experience. Jeff became solidly impressed with the clinical need for a practical ambulatory recorder and data reduction system. A few weeks later at a national meeting of the Institute of Electrical and Electronics Engineers (IEEE) Computer Society (12), he announced that “since over half of the patients with serious arrhythmias are not aware of them, this instrument is being redeveloped to record prolonged periods of electrocardiographic observations, so it can become a convenient and useful apparatus to detect serious life-threatening arrhythmias in time for aggressive therapeutic management.”

I realized that this dynamic monitor was the missing link needed to enlighten those who had become aware of daily news reports of sudden deaths possibly due to arrhythmias, but who had learned from the popular press that these fatalities could be prevented if treated prophylactically with appropriate antiarrhythmic agents and electrical defibrillation within what we named “the narrow 4 min time limit” (34). This latter determination led my small Cedars of Lebanon research staff into our new clinical concept of aggressive management for the coronary victim (35), which ultimately reduced the coronary mortality rate in the United States by approximately 40% in the ensuing 30 years (36).

Because of the enthusiasm and aggressive interest demonstrated by me and my research staff in identifying the patient at risk of sudden cardiac death triggered by ventricular fibrillation, Jeff sent Willford Glasscock to visit us at Cedars of Lebanon Hospital in Los Angeles to demonstrate the miniaturized electromagnetic tape camera and how to integrate the taped recording of a patient’s time clock and diary with the more comprehensive data reduction systems. Glasscock’s audiovisual superimposed ECG presentation (AVSEP) data reduction system (Fig. 5) provided a fast cathode tube display, which superimposed QRST complexes and displayed an audible arrhythmia picket fence display of each RR interval that would change its pitch and alert the reader to possible alterations in rate and rhythm that could also be recorded on transcription of ECG paper readouts. About that time, Hellerstein and Friedman (37) recommended a complete readout for full disclosure of every ECG complex over prolonged time intervals. It soon became evident that this concept had considerable clinical merit.

Proposed Clinical Potentials for the Expanded Applications of Ambulatory ECG Monitoring

When the first clinical prototype became available in 1962, our investigative group, led by Drs. Tzu-Wang Lang, Harold Bernstein and Herbert Gold, rushed to test it on puzzling clinical problems in patients suspected of having recurrent symptoms of remote insufficiency (28-30,32,33). After several years of rewarding clinical studies we narrowed the potential uses of our ambulatory monitor to the following: 1) to determine the origin of undefined, distressing...
and remote clinical symptoms experienced by the patient during customary daily activities; 2) to detect, classify and manage disturbing recurring cardiac arrhythmias; 3) to locate and confirm the extent, duration and seriousness of arrhythmic or ischemic events; 4) to correlate puzzling clinical signs and symptoms that can cause recurring phantom-like pathophysiologic disorders of remote target organs (cardiac, cerebral, renal, splanchnic and peripheral vasculature); 5) to provide for better prognostication, prediction and prevention after definitive diagnostic evaluation; 6) to document the therapeutic need and permit prescription of the most favorable and appropriate pharmacologic agents or pacemaker for specific clinical conditions; and 7) to provide new research logistics for clinical pharmaceutical trials, including determination of long-term efficacy of anti-ischemic and antiarrhythmic agents.

The electrocardiocorder and data reduction system became ready for manufacture. News of the new device attracted considerable attention after the first clinical prototype became available in 1961 and I was swamped by numerous inquiries from both potential manufacturers and users. By 1962 when the clinical need for an effective accurate ambulatory ECG monitor and readout system was even more apparent, I phoned Jeff to begin looking for a manufacturer. When Jeff failed in his attempt to find a manufacturer, I introduced him to Bruce Del Mar, who in previous years had helped us considerably with the development of electromagnetic flowmeters. Del Mar's capable engineers were soon prepared to build this marketable electrocardiocorder “from stem to stern,” and Del Mar Avionics continues to manufacture the Holter monitor to this day. I was confident that the system would become an important clinical diagnostic instrument, but I never dreamed that this small instrument would earn the megabillion income in clinical practice that it did in the ensuing 30 years.

Clinical Trials of the New Ambulatory ECG Data Reduction System

As soon as the new ambulatory monitor was commercially released, we considered ourselves fortunate when the editors of New Physician of the American Medical Association invited my research staff to publish a series of short clinical reports. This monthly feature was intended to provide interesting teaching material, describing ECG and other clinical phenomena, some of which could be documented by the Holter ambulatory monitor (38-42). This also provided us with ample opportunity to publish our revolutionary concepts of clinical insufficiency states.

Clinical applications. We then began a series of comprehensive electrophysiologic and hemodynamic investigations using the Holter data reduction system to determine and validate efficacy, to learn the pitfalls of standard coronary intensive care fixed monitoring systems and to prove the need or clinical potential of lifesaving defibrillators, pharmacologic agents and pacemakers (28-33,38-43). These clinical observations resulted in 29 publications, 8 scientific exhibits and numerous presentations at major medical meetings during the next 10 years. We accomplished most of our primary objective—to provide disclosure readouts of the ECG data, which for the first time could provide dynamic but invaluable patient data to document and certify the aggressive management of the coronary victim. The Holter monitor soon became a practical clinical instrument. We also applied this system to monitor the evanescent effects of anesthesia and associated surgical maneuvers. This included the observation in 1967 by Kumer et al. (44) that 60% of noncardiac patients developed serious arrhythmias or conduction defects during routine anesthesia.

The Holter monitor. We were then able to describe many promising clinical applications based on ECG monitoring and more appropriate pathophysiologic and hemodynamic studies and finally substantiated by necropsy, some of which we featured in our clinical report in JAMA, “Detection of phantom arrhythmias and evanescent electrocardiographic abnormalities” (28). In that publication, we used the terms “phantom arrhythmias” and “Holter monitor” for the first time to describe some remote precipitating insufficiency states that needed emergency management. Our publication also gave the system a new identity by my naming it the “Holter monitor,” which replaced what we considered the meaningless title of “dynamic electrocardiocorder.”

Automatic evaluation of the character and frequency of ectopic heart rhythms. We first used our personal observations as the reference standard for counting and validating the number and character of all ectopic beats occurring during the recording of 8 h test tapes. We soon realized that the proposed as “new automatic” electrocardiocorder systems led to many misleading inaccuracies, despite strong advertising claims that they provided accurate readouts. We became aware that the automatic arrhythmia sensors and totalizers were providing misleading answers because they often could not differentiate whether the arrhythmia was supraventricular or ventricular or due to conduction defects, mainly because they were incapable of differentiating atrial or ventricular from junctional rhythms. The atrial complexes were usually of such low voltage that they could not be clearly identified in the electromagnetic recording. To train coronary care technical staffs, we set up test tapes with known numbers of ectopic beats, but the debate continued whether the differentiation could be made to provide an accurate, real-time, automatic, hands-off measurement of ectopic beats.

I realized from the beginning that this ambulatory diagnostic system would be a rewarding investment for any manufacturer and prophesized its maximal success, “like shooting ducks in a barrel.” After this initial impetus, I thought it curious that it took more than 10 years for the medical profession to fully realize the potential clinical benefits of the Holter monitoring system. I continued to explain its usefulness in numerous lectures, exhibits at
medical conventions and publications for nearly 9 years until the profession showed a distinct interest. At present, I am amazed that the commercial market for Holter equipment and diagnostic readout services has been estimated at > $750 million per year. However, I am greatly disappointed that my volunteer research efforts, which cost me a fortune, were not considered favorably by those manufacturers I helped when they charged me full price for my purchases of expensive Holter systems for my research laboratory, thus adding insult to injury.

Naming the new ambulatory monitoring system. At the time Jeff and I worked together, he insisted that the device be called the Holter-Corday system. My friends still remind me that they thought I was foolish for turning down Jeff’s request to share the authorship with him because they considered my scientific contributions relatively significant. However, I am more than proud that I had the opportunity to participate in the perfection of the first practical ambulatory monitor system for cardiovascular studies, mostly based on the physiologic and clinical data generated and validated in my research laboratory over a period of years.

Final Grand Rounds. When I completed 10 years of clinical trials with the Holter monitor at the Cedars of Lebanon Hospital, I was invited by the medical staff to present Grand Rounds on the subject of the diagnostic ambulatory monitor. I believed that we had provided the missing link for a marketable system that would aid the clinician, but at the end of my presentation the chairman of the session summarized his opinion by saying that the ambulatory monitor was a waste of time and had very little, if any, clinical potential.

I thank Joan Holler for graciously providing me with documentation and anecdotal information regarding her late husband; I also thank Wilford Glasscock for his time and effort researching the files at the Montana Historical Society to provide me with facts. Several early investigators on the coronary circulation and electrocardiography have contributed much to our understanding of coronary disease.

References

41. Corday E, Lang TW, Rosett E, Vyden JK. URG of the month.